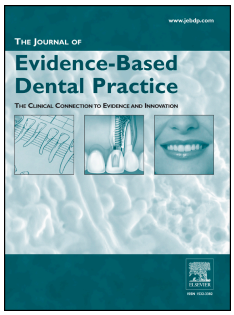
Blakey K, McNally RJ.

Declarative Title: Fluoridation may not be linked with adverse health outcomes.

***The Journal of Evidence-Based Dental Practice* (2016)**

DOI: 10.1016/j.jebdp.2016.09.009

Accepted Manuscript



Declarative Title: Fluoridation may not be linked with adverse health outcomes

Karen Blakey, BSc, Research Assistant, Richard J.Q. McNally, BSc, MSc, DIC, PhD, Reader in Epidemiology

PII: S1532-3382(16)30132-4

DOI: 10.1016/j.jebdp.2016.09.009

Reference: YMED 1146

To appear in: *The Journal of Evidence-Based Dental Practice*

Please cite this article as: Blakey K, McNally RJQ, Declarative Title: Fluoridation may not be linked with adverse health outcomes, *The Journal of Evidence-Based Dental Practice* (2016), doi: 10.1016/j.jebdp.2016.09.009.

Article Analysis and Evaluation / Etiology/Other

DECLARATIVE TITLE:

Fluoridation may not be linked with adverse health outcomes

ARTICLE TITLE AND BIBLIOGRAPHIC INFORMATION

Community water fluoridation and health outcomes in England: a cross-sectional study

Young N, Newton J, Morris J, Morris J, Langford J, Iloya J, Edwards D, Makhani S, Verne J.

Community Dent Oral Epidemiol 2015;43:550-9

REVIEWERS

Karen Blakey, BSc

Richard J.Q. McNally, BSc, MSc, DIC, PhD

PURPOSE/QUESTION

Does exposure to water from artificial fluoridation programs lead to positive or negative health outcomes?

SOURCE OF FUNDING

Public Health England

TYPE OF STUDY/DESIGN

Ecological (area-based)

LEVEL OF EVIDENCE

Level 2 Limited quality, patient-oriented evidence

STRENGTH OF RECOMMENDATION GRADE

Not applicable

SUMMARY

Subjects

This was an ecological study and included all children and adults living in England, excluding those resident in areas where the naturally occurring fluoride level was close to 1 part per million (ppm).

Key Risk/Study Factor

The key study factor was community water fluoridation. The exposure of interest was residence in an area where the fluoride level in water supply has been adjusted (artificially fluoridated).

Main Outcome Measures

Prevalence of dental caries in children, admission rates for tooth extraction in children' incidence of hip-fracture, renal stones, Down syndrome, any cancer, osteosarcoma or bladder cancer' death from any cause.

Main Results

Children living in artificially fluoridated areas had a lower prevalence of dental caries ($P < 0.001$), fewer affected teeth ($P < 0.001$), and lower admission rates for extraction of teeth (55% lower; 95% confidence interval [CI] -73%, -27%; $P = 0.001$). There were negative associations between residence in an artificially fluoridated area and incidence of renal stones (7.9% lower; 95% CI -9.6%, -6.2%; $P < 0.001$) and bladder cancer (8.0% lower; 95% CI -9.9%, -6.0%; $P < 0.001$). There was no evidence for associations between fluoridation and nondental health outcomes such as hip fracture, Down syndrome, osteosarcoma, all-cancer, or all-cause mortality.

Conclusions

The authors concluded that their study provides reassurance that fluoridation programs are a safe and highly effective way to provide a population with the protective dental health property of fluoride. The study found lower rates of nondental outcomes in areas of artificial fluoridation. However, the authors stated that the ecological study design did not allow any conclusions to be drawn with regard to the potential protective effect of fluoridation for nondental outcomes.

COMMENTARY AND ANALYSIS

Fluoride occurs naturally in drinking water supplies, although there is variation in concentration. Populations that have high levels of naturally occurring fluoride in their drinking water have been observed to have low levels of dental caries.[1] The range for maximum dental health benefit is 0.7 to 1.2 ppm. Levels below 0.3 ppm may not confer any benefit.[2]

The recognition that there was an association between dental caries prevalence and socioeconomic deprivation led to the introduction of artificial fluoridation in some parts of Great Britain.[3] At present, artificial fluoridation is carried out by five water companies.[4] The fluoride level is mainly increased through adding hexafluorisicilic acid, a by-product of the aluminum industry, to a Water Supply Zone (WSZ) that has been fitted with the appropriate pumping equipment.[5]

Fluoridation programs have been credited by the US Centers for Disease Control and Prevention as one of the ten great public health achievements of the 20th century.[6] However, there is also much opposition to implementation on the basis that the addition of fluoride to community water supplies may lead to negative health effects such as an increased risk of cancer and in particular the bone cancer osteosarcoma.[7,8]

Systematic reviews have been carried out to assess the efficacy and dental and nondental health impact of community fluoridation programs. The main conclusions remain the same: artificial fluoridation is a cost-effective way of providing a community with the dental health benefit of fluoride but such a conclusion is based on medium to low quality research in the hierarchy of scientific evidence.[9,10,11]

Given that whole communities are subject to fluoridation programs and avoidance is impossible in those areas in which they operate, it remains important to strengthen the evidence base in relation to their efficacy and effectiveness of reducing inequalities in dental health as originally intended.[12]

A previous ecological study analyzed the association between fluoride in drinking water and the incidence of the two main types of bone cancer that affect children and young adults--osteosarcoma and Ewing sarcoma.[8] That study used data from the

whole of Great Britain (GB) for the period 1980–2005. Similar to Young et al.'s[13] study that is under review here, Blakey et al.[8] did not find evidence of an association between bone cancer incidence and level of fluoride in drinking water. However, the authors also had to apply cautionary caveats given that it was a small area analysis and susceptible to the ecological fallacy.[14] Finding no association could have been due to biases such as exposure measurement error or lack of data availability rather than a true relationship between the exposure data and the two outcome measures.

Nevertheless, Blakey et al.[8] was the first large national study of its kind and therefore application of the ecological design was appropriate for such an initial investigation of etiological hypotheses.[15] Furthermore, the authors developed and used novel GIS methodologies to enable a fluoride level in drinking water across the whole of GB to be assigned to each small area unit in GB. Analyzing the fluoride levels using individual sampling data taken from WSZs showed that 33% of artificially fluoridated WSZs in England were supplying water that was below 0.7 ppm of fluoride, the lower limit of the optimal level for dental health benefit. There were no artificial fluoridation programs operating in Scotland and Wales.

This was a very important finding with regard to the investigation of the safety and effectiveness of artificial fluoridation programs, particularly in England, but could also be applicable in any other country that artificially fluoridates all, or part, of their drinking water supply. Such heterogeneity in artificially fluoridated areas and such a large proportion of WSZs being dosed to a level considered sub-optimal for a dental benefit strongly suggests that studies investigating the effectiveness of fluoridation programs are seriously flawed. The fluoride level in artificially fluoridated areas may not truly be dosed to 1 ppm. The further implication is that studies that have previously adopted a binary analysis approach between artificial and naturally occurring fluoridated areas are fundamentally flawed.

Young et al.[13] reports the results of an ecological study from part of England. The authors concluded that the ecological nature of the study design did not permit any substantive conclusions to be drawn with regard to putative protective nondental health effects of water fluoridation. The authors used residence in an area that was artificially fluoridated as the measure of exposure. This was treated as a binary variable and so did not permit any further assessment of associations with the actual

fluoride levels. They excluded areas where natural fluoride levels were close to 1 ppm, although the actual critical value was not specified. No attempt to assess the actual levels of exposure within the selected areas was made. Given Blakey et al's[8] findings discussed above, this is a serious limitation of the study.

Another methodological shortcoming is related to the outcome data. In particular, the dental health survey data[16] have been measured at a very low resolution, that is, Local Authority level (upper tier and lower tier) and bring further potential misclassification. Such a low level of resolution has a much higher chance of masking differences. It makes it impossible to report true findings at a higher level of resolution such as Lower Super Output Area (LSAO). Some of the variables, such as mean number of missing teeth (mean mt [% mt > 0]) are based on fewer than 30 volunteers. The sampling methodology is also seriously at risk of selection bias.[17]

Although not cited by the authors, the Young et al.[13] study is directly linked to the Public Health England water fluoridation health monitoring report for England that was published in March 2014.[18] The McGrady et al.[19] study was included and reported as one of the study's health indicators in the health monitoring report. McGrady et al.[19] found that fluorosis (mottling of teeth caused by too much fluoride intake)[1] was more prevalent in areas subject to artificial fluoridation programs when compared to areas that didn't add fluoride. However, Young et al.[13] does not make reference to the fact that McGrady et al.[19] found increased risk of developing mild fluorosis was associated with residence in an artificially fluoridated area. Instead, Young et al.[13] highlights both areas (the artificially fluoridated city Newcastle and non-artificially fluoridated city of Manchester) demonstrated a low prevalence of moderate and severe forms of dental fluorosis.

The Young et al.[13] study reported protective effects for dental caries, renal stones, and bladder cancer. The authors acknowledged that the association found for bladder cancer may not truly reflect an individual protective effect (the ecological fallacy). Furthermore they state that there is potential for misclassification of exposure status due to the study design. However, the authors make a strong statement relating to decreased prevalence of dental caries in areas of artificial fluoridation. They state that "fluoridation is a safe and highly effective public health measure to reduce dental decay".[13] The study cannot provide reassurance that

artificial fluoridation programs are safe and highly effective given there are so many potential sources of misclassification.

The authors should be more cautionary with regard to the interpretation of their results for a number of other reasons. For example, the original ecological studies that detected an association between fluoride and prevention of dental caries were from a previous era and do not necessarily reflect the present day availability of other sources of fluoride intake, for example, via tea, bony fish, and fluoridated toothpaste. Fluoridated toothpaste did not come into widespread use until the early 1970s.[4]

One of the other major methodological flaws that should not be overlooked is the issue of non-contiguous area boundaries that were subject to change over time. Census boundaries can change over time and some changes can be quite substantial.[20] Blakey et al.[8] adjusted both numerator data (geo-referenced bone cancer registration data) and denominator data (Population census data) so they were compatible with 2001 census definitions.[21] Blakey et al.[8] used a time series of Townsend Deprivation scores that had adjusted all boundaries so they were compatible with 2001 census boundaries as a measure of social deprivation.[22] Young et al.[13] used the Index of Multiple Deprivation with no adjustment.

Similarly, WSZs are non-contiguous with the census zones and were also subject to change over time given that they are defined according to a maximum population threshold.[23] This means that a number of WSZs can supply the residents of a LSOA and the residential property can be subject to water supply from different WSZs over time. It is not clear whether Young et al.[13] allows for this confounding factor.

In summary, the authors have conducted a limited study of links between fluoride and health outcomes in part of England. There are major methodological shortcomings, not only in the design but also with regard to the measure of exposure to fluoride. Binary analysis was not an appropriate way of assessing exposure to fluoride given the heterogeneity within areas where artificial fluoride programs are operating. It is not possible to make firm conclusions about the effectiveness and safety of artificial fluoridation from the Young et al.[13] study. Studies that use binary analysis merely perpetuate the questions regarding the effectiveness and safety of artificial fluoridation programs rather than answering them. Given the controversy

and the lack of high-quality research, a substantial investment in further studies is required so that individual exposure can be taken into consideration.

REFERENCES

1. Ainsworth N. Mottled teeth. Br Dent J 1933;55:233-50.
2. Harrison PT. Fluoride in water: a UK perspective. J Fluor Chem 2005;126:1448-56.
3. Pizzo G, Piscopo MR, Pizzo I, Guiliana G. Community water fluoridation and caries prevention: a critical review. Clin Oral Invest 2007;11:189-93.
4. Mullen J. European Association for Paediatric Dentistry. History of water fluoridation. Br Dent J 1995;199(Suppl 7):1-4.
5. The Stationary Office. Water Industry Act 1991. Chapter 56. The Stationary Office. [Available online at URL: http://www.legislation.gov.uk/ukpga/1991/56/pdfs/ukpga_19910056_en.pdf Accessed 16/09/2016].
6. CDC. Ten Great Public Health Achievements - United States, 1900-1999. MMWR. 1999: 48: 241-3. [Available online at URL: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5727a1.htm Accessed 16/09/2016]
7. Committee to Coordinate Environmental Health and Related Programs, Ad Hoc Subcommittee on Fluoride. Review of Fluoride: Benefits and Risks. Washington, DC: Public Health Service, Department of Health and Human Services, 1991.
8. Blakey K, Feltbower RG, Parslow RC, James PW, Gomez Pozo B, Stiller C, Vincent TJ, Norman P, McKinney PA, Murphy MF, Craft AW, McNally RJ. Is fluoride a risk factor for bone cancer? Small area analysis of osteosarcoma and Ewing sarcoma diagnosed among 0-49-year-olds in Great Britain, 1980-2005. Int J Epidemiol 2014;43:224-34.
9. McDonagh MS, Whiting PF, Wilson PM, Sutton AJ, Chestnutt I, Cooper J, Misso K, Bradley M, Treasure E, Kleijnen J. Systematic review of water fluoridation. BMJ 2000;321:855-9.
10. Yeung CA. A systematic review of the efficacy and safety of fluoridation. Evid Based Dent 2008;9:39.

11. Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, Alam R, Tugwell P, Welch V, Glenny AM..Water fluoridation for the prevention of dental caries. Cochrane Database of Systematic Reviews 2015, Issue 6. [Available online at URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010856/epdf Accessed 16/09/2016]
12. British Dental Association. The British Dental Association Oral Health Inequalities Policy. The British Dental Association. 2009. [Available online at URL: https://www.bda.org/dentists/policy-campaigns/public-health-science/public-health/Documents/oral_health_inequalities_policy.pdf Accessed 16/09/2016].
13. Young N, Newton J, Morris J, Morris J, Langford J, Iloya J, Edwards D, Makhani S, Verne J. Community water fluoridation and health outcomes in England: a cross-sectional study. Community Dent Oral Epidemiol 2015;43:550-9.
14. Greenland S, Robins J. Invited commentary: ecological studies – biases, misconceptions, and counterexamples. Am J Epidemiol 1994;139:747–60.
15. Wakefield J. Ecologic studies revisited. Annu Rev Public Health. 2008;29:75–90.
16. Public Health England. National Dental Epidemiology Programme for England: oral health survey of five-year-old children 2012. A report on the prevalence and severity of dental decay. 2013. [Available online at URL: http://www.nwph.net/dentalhealth/Oral%20Health%205yr%20old%20children%202012%20final%20report%20gateway%20approved.pdf Accessed 16/09/2016].
17. Glenny AM, Worthington HV, Milsom KM, Rooney E and Tickle M. BMC Medical Research Methodology 2013. 13:108. [Available online at URL: http://bmcmedresmethodol.biomedcentral.com/track/pdf/10.1186/1471-2288-13-108?site=bmcmedresmethodol.biomedcentral.com Accessed 16/09/2016].
18. Public Health England. Water fluoridation: Health monitoring report for England 2014. HMSO. [Available online at URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/300202/Water_fluoridation_health_monitoring_for_england__full_report_1Apr2014.pdf Accessed 16/09/2016].

19. McGrady MG, Ellwood RP, Maguire A, Goodwin M, Boothman N, Pretty IA. The association between social deprivation and the prevalence and severity of dental caries and fluorosis in populations with and without water fluoridation. BMC Public Health, 2012. 12: p. 1122. [Available online at URL: http://bmcpublichealth.biomedcentral.com/track/pdf/10.1186/1471-2458-12-1122?site=bmcpublichealth.biomedcentral.com Accessed 16/09/2016].
20. Simpson L. Geography conversion tables: a framework for conversion of data between geographical units. Int J Popul Geog 2002;8 69–82.
21. Norman P, Rees P, Boyle P. Achieving data compatibility over space and time: creating consistent geographical zones. Int JPopul Geog 2003;9:365–86.
22. Norman P. Identifying change over time in small area socioeconomic deprivation. Appl Spatial Anal Policy 2010;3:107–38.
23. Drinking water quality in England: The position after 25 years of regulation. A report by the Chief Inspector of Drinking Water. DWI. 2015. [Available online at URL: http://dwi.defra.gov.uk/about/annual-report/2014/sum-eng.pdf Accessed 16/09/2016].

REVIEWERS

Karen Blakey, BSc

Research Assistant

Institute of Health & Society

Newcastle University

Sir James Spence Institute

Royal Victoria Infirmary

Queen Victoria Road

Newcastle upon Tyne NE1 4LP

Phone: 0191 2821347

karen.blakey@ncl.ac.uk

Richard J.Q. McNally, BSc, MSc, DIC, PhD

Reader in Epidemiology

Institute of Health & Society

Newcastle University

Sir James Spence Institute

Royal Victoria Infirmary

Queen Victoria Road

Newcastle upon Tyne NE1 4LP

Phone: 0191 2821356

richard.mcnally@ncl.ac.uk